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ORIGINAL ARTICLE

Remifentanil increases the incidence of mesenteric traction syndrome: preliminary randomized controlled trial

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Abstract
Purpose The use of remifentanil is often associated with the observation of mesenteric traction syndrome (MTS) soon after manipulation of the intestine during abdominal surgery. MTS symptoms include facial flushing, hypotension, and tachycardia. In the study reported here, we prospectively investigated the effects of remifentanil on the incidence of MTS in abdominal surgery.
Methods One hundred patients scheduled for abdominal surgery were randomly assigned to two groups. In one group (n = 50), fentanyl alone was used as intravenous analgesic (control, group C); in the second group (n = 50), both fentanyl and remifentanil were used (remifentanil group, group R). In all patients, anesthesia was induced with propofol and rocuronium and then maintained with sevoflurane inhalation. Remifentanil was continuously infused for patients in group R as an analgesic. Plasma concentration of 6-keto-$PGF_{1\alpha}$ was measured before surgery and 20 min after the skin incision was made in six patients of group R and seven patients of group C.
Results MTS occurred in 20 cases in group R (40.0%), but in only five cases in group C (10.0%). In both groups, the incidence of MTS was higher in laparotomy than in laparoscopic surgery. The plasma concentration of 6-keto-$PGF_{1\alpha}$ was low in both groups before surgery and was elevated 20 min after skin incision in both groups in patients in whom MTS appeared.
Conclusions The results of this study suggest that the use of remifentanil in laparotomy facilitates MTS.

Keywords Remifentanil · Mesenteric traction syndrome · Prostacyclin · 6-Keto-$PGF_{1\alpha}$

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Introduction

Mesenteric traction syndrome (MTS) is described as facial flushing, frequently with hypotension and tachycardia. Several reports have suggested that the incidence of MTS is as high as 30–85% in patients undergoing aortic abdominal aneurysm resection or major abdominal surgery [1–5]. Traction of the intestine or intraabdominal traction on the mesentery results in increased shear stress on endothelial cells of mesenteric vessels and the production of prostacyclin (PGI_2), followed by activation of cyclooxygenase (COX) [1, 2, 6]. PGI_2 release following mesenteric traction induces systemic vasodilation [7]. A recent publication suggested that not only PGI_2 but also histamine released from mesenteric mast cells may also cause MTS [8]. Pretreatment with non-selective COX inhibitors, such as ibuprofen or aspirin, has been found to prevent the PGI_2 release associated with mesenteric traction [2, 3, 7, 9]. H_1 and H_2 antihistamines are also prophylactic drugs [8].

Remifentanil is a short-acting μ-opioid agonist, and its use during surgery can lead to hemodynamic stability. Remifentanil plays an important role in analgesia during general anesthesia administration. We noticed that the incidence of facial flushing and hemodynamic changes soon after the incision increased in abdominal surgery with the use of remifentanil. It has also been reported that PGI_2

production may be induced by remifentanil in vitro [10]. To date, however, it is not clear whether the incidence of MTS is increased by the use of remifentanil and whether the cause of MTS by remifentanil is PGI_2.

A retrospective record review of abdominal surgery and abdominal aortic aneurysm surgery (396 patients) between January 1, 2007 and October 1, 2007 was performed in our hospital. Facial flushing was recorded in 10.8% of the patients under general anesthesia with remifentanil, but in only 2.4% of patients not treated with remifentanil.

In the study reported here, we prospectively assessed whether the use of remifentanil affected the incidence of MTS in abdominal surgery.

Methods

This was a single-center, open-label study performed between February and July 2008. One hundred adult patients [American Society of Anesthesiologists physical status (ASA-PS) 1–2] scheduled for abdominal surgery under general anesthesia were investigated in this prospective study. Our institutional ethics committee approved the protocol of this study, and written informed consent was obtained from each patient. Patients were randomized to two groups: 50 patients to the control group (group C) and 50 to the remifentanil group (group R). Patients medicated with non-steroidal antiinflammatory drugs (NSAIDs) were excluded from the study.

An epidural catheter was inserted before the induction of anesthesia and located between Th7 and L3. General anesthesia was then induced with propofol 1–2 mg/kg combined with the inhalation of sevoflurane in oxygen and rocuronium 0.6 mg/kg. The patients in group C received fentanyl alone as analgesic, whereas group R patients received an intravenous injection of fentanyl and a continuous intravenous infusion of remifentanil. Anesthesia was maintained with sevoflurane and fentanyl in all patients, with group R patients also receiving a remifentanil infusion. The bispectral index (BIS) was used as a measure of the degree of sedation, and the values of BIS were controlled between 40 and 60. Dosages of remifentanil were 0.1–0.5 μg/kg/min for induction, and 0.1–0.3 μg/kg/min during maintenance of anesthesia. Anesthetic drugs for epidural anesthesia, such as morphine and local anesthetics, were administered 30 min after skin incision, after hemodynamic stability had been achieved.

Arterial blood was taken from 13 randomly selected laparotomy (open abdominal surgery) patients for the measurement of 6-keto-$PGF_{1\alpha}$ immediately before surgery and 20 min after skin incision. The concentration of 6-keto-$PGF_{1\alpha}$ was measured by radioimmunoassay (SRL, Tokyo, Japan).

All patients were assigned to Levels 1 or 2 according to modified Koyama's classification of MTS [11]. Compared with their hemodynamic state before skin incision, Level 1 patients had facial flushing ranging from slight to moderate, while Level 2 patients manifested complete facial flushing with concomitant hypotension and tachycardia. Each anesthesiologist assessed the presence of MTS or not based on the symptoms after the skin incision had been made. We retrospectively reviewed each anesthetic record to confirm the presence or absence of MTS.

Data were analyzed using the Mann–Whitney U test, χ^2 test, and Fisher's exact test and statistical analysis software (SPSS for Windows; SPSS Japan, Tokyo, Japan). Results were expressed as the mean ± standard deviation (SD). For all determinations, p values of <0.05 were considered to be statistically significant.

Results

Demographic data for both groups are summarized in Table 1. There was no significant difference in age, height, sex ratio, or surgical procedure between the groups; body weight and body mass index (BMI) were significantly different between groups. There were 33 and 34 laparotomies in group R and C, respectively. The types of surgery are also given in Table 1.

The incidence of MTS in this study is illustrated in Fig. 1. MTS was observed in 20 of the 50 patients in group R and in five patients of the 50 in group C. As shown in Fig. 1, MTS appeared more often in laparotomy (group R, 54.6%; group C, 11.8%) than in laparoscopic surgery (group R, 11.8%; group C, 6.3%). There were 14 and three cases of MTS classified as Level 2 during laparotomy [11] in group R and group C, respectively, but laparotomy was performed at almost the same frequency in both groups (group R; 78%, group C; 75%) (Fig. 2).

In most cases of MTS, facial flushing was observed within 20 min (mean ± SD; 16 ± 5 min in group R, 16 ± 4 min in group C; $p = 0.962$) of making the skin incision, just when mesenteric manipulation started. The mean duration of facial flushing was 30 ± 18 min in group R and 21 ± 11 min in group C ($p = 0.376$). There was no significant difference in the dosage of remifentanil and sevoflurane between patients with or without MTS, respectively. In group C, the dosage of fentanyl at 30 min after the skin incision had been made was larger in the cases of patients with MTS [MTS (+)] than in patients without MTS [MTS (−)] (Table 2).

In cases of laparotomy in which MTS appeared, the mean reduction in blood pressure was 49.0 ± 22.8 mmHg in group R patients and 58.3 ± 41.2 mmHg in group C patients, and the mean elevation in the heart rate was

Table 1 Patient demographics and types of surgery

Patient demographics	Group C ($n = 50$)	Group R ($n = 50$)	p value
Age (years)	64.7 ± 12.6	65.8 ± 12.0	NS
Height (cm)	160.9 ± 6.5	162.9 ± 9.7	NS
Weight (kg)	55.9 ± 8.2	61.1 ± 12.0	0.013*
BMI (kg/m^2)	21.6 ± 2.7	22.9 ± 3.3	0.031*
Male/female	35/15	36/14	NS
Surgery (laparotomy/laparoscopy)	34/16	33/17	NS
Types of surgery (cases)			
Gastrectomy	19	18	NS
Colectomy	20	18	
Hepatectomy	7	6	
Pancreaticoduodenectomy	2	4	
Others[a]	2	4	

n Number of patients, *NS* not significant, *BMI* body mass index, *Group C* control group (fentanyl alone as intravenous analgesic), *Group R* remifentanil group (fentanyl and remifentanil were used as intravenous analgesic)

* $p < 0.05$ was considered to be significant. Each value of group C was compared with the value of group R

Data are given as the mean ± standard deviation

[a] Others denotes lymphadenectomy, duodenectomy, and closure of stoma

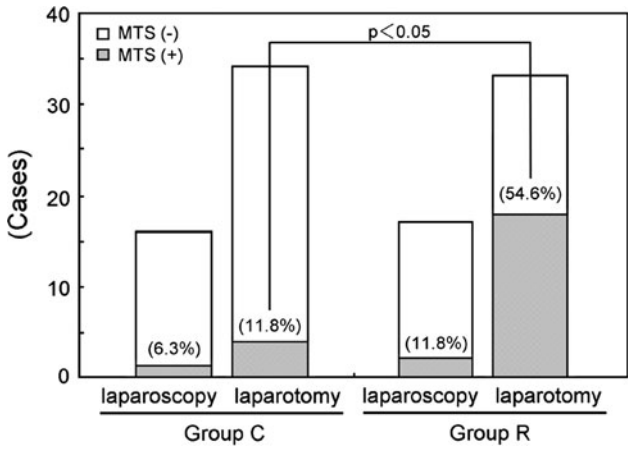

Fig. 1 Total incidence of mesenteric traction syndrome (MTS) (%) among laparoscopic surgeries and laparotomies

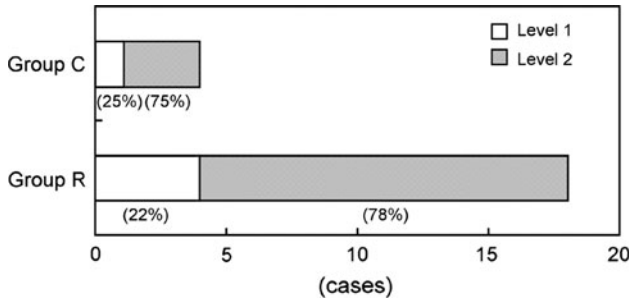

Fig. 2 Incidence of MTS with laparotomy in each group according to modified Koyama's criteria

14.9 ± 16.2 per min in group R and 19.3 ± 11.4 per min in group C (Table 3).

The plasma concentration of 6-keto-PGF$_{1\alpha}$, a stable metabolite of PGI$_2$, was measured before surgery and 20 min after the skin incision had been made in 13 patients. Table 4 shows the profiles of all cases in which the plasma concentration of 6-keto-PGF$_{1\alpha}$ was examined. Of the 13 randomly chosen patients, MTS occurred in five of six patients in group R (83.3%), but in only two of seven patients in group C (28.6%). There was no difference in the mean plasma concentration of 6-keto-PGF$_{1\alpha}$ before skin incision between groups (Fig. 3). The concentration of 6-keto-PGF$_{1\alpha}$ at 20 min after the skin incision had been made tended to increase more frequently in group R patients than in group C patients. In cases in which MTS appeared, the plasma 6-keto-PGF$_{1\alpha}$ was increased not only in group R (mean values ± SD, pre: 20.9 ± 6.4 pg/mL, post: 1464.0 ± 526.8 pg/mL, $p = 0.021$), but also in group C (mean values, pre: 22.5 pg/mL, post: 1850.0 pg/mL) (Fig. 3). The relationship between the plasma concentration of 6-keto-PGF$_{1\alpha}$ and the levels of MTS was not apparent (Table 4).

Discussion

The aim of this study was to investigate whether remifentanil affected the occurrence of MTS in patients undergoing abdominal surgery under general anesthesia using sevoflurane. We demonstrated that the incidence of MTS was higher in group R than in group C patients.

Several reports have suggested that the incidence of MTS is as high as 30–85% in patients undergoing aortic

Table 2 Comparison of intraoperative variables in both groups in laparotomy

Anesthesia	Group C ($n = 34$)		p value	Group R ($n = 33$)		p value
	MTS (−) ($n = 30$)	MTS (+) ($n = 4$)		MTS (−) ($n = 15$)	MTS (+) ($n = 18$)	
Fentanyl (μg/kg)	3.1 ± 1.2	5.2 ± 1.6*	0.004	1.0 ± 0.7	0.9 ± 0.8	NS
Remifentanil (μg/kg/min)	–	–		0.17 ± 0.05	0.17 ± 0.06	NS
Sevoflurane (%)	1.9 ± 0.3	1.8 ± 0.3	NS	1.8 ± 0.3	1.9 ± 0.3	NS

$p < 0.05$ was considered significant. Each value of MTS (+) was compared with the value of MTS (−), respectively

Data are given as the mean ± standard deviation

MTS Mesenteric traction syndrome, *MTS (+)* cases of patients with MTS, *MTS (−)* cases of patients without MTS

Table 3 Comparison of intraoperative hemodynamics between both groups in terms of MTS (+) cases in laparotomy

Intraoperative hemodynamics	Group C		Group R		p value
	Pre	MTS	Pre	MTS	
sBP	156.7 ± 38.0	99.7 ± 20.1	130.6 ± 27.2	81.6 ± 17.4	
Δ		58.3 ± 41.2		49.0 ± 22.8	NS
dBP	85.3 ± 8.3	54.7 ± 10.8	76.1 ± 15.7	50.1 ± 12.9	
Δ		32.3 ± 15.5		26.1 ± 13.2	NS
Heart rate	80.0 ± 13.1	99.3 ± 13.9	65.1 ± 11.8	80.0 ± 18.4	
Δ		19.3 ± 11.4		14.9 ± 16.2	NS

$p < 0.05$ was considered to be significant. Each value of group C was compared to group R, respectively.

Data are expressed as the mean ± SD

pre Before skin incision, *MTS* when MTS appeared, *sBP* systolic blood pressure, *dBP* diastolic blood pressure, *Δ* differences between pre and post

Table 4 Plasma concentrations of 6-keto-$PGF_{1\alpha}$ before (pre) and during (post) operation

Groups	MTS[a]	Age (years)	Sex	Surgical procedure	Hemodynamic change	6-keto-$PGF_{1\alpha}$ (pg/mL)	
						Pre	Post
Group C	+	68	M	Distal gastrectomy	+	23	1100
		67	M	Colectomy	−	22	2600
	−	69	M	Cholecystectomy		24	58
		68	M	Distal gastrectomy		27	1400
		81	F	Colectomy		27	30
		57	M	Hepatic tumor resection		15	560
		67	M	Total gastrectomy		14	220
	Mean ± SD					21.7 ± 5.3	852.6 ± 931.7
Group R	+	70	M	Cholecystectomy	−	10	920
		81	F	Distal gastrectomy	+	25	1700
		73	M	Proctosigmoidectomy	+	25	2200
		77	F	Pancreaticoduodenectomy	+	23	1500
		80	M	Distal gastrectomy	−	22	1000
	−	66	M	Colectomy and cholecystectomy		17	160
	Mean ± SD					20.3 ± 5.8	1246.7 ± 710.9
p value						NS	NS

$p < 0.05$ was considered to be significant, Each value of group C was compared with the value of group R, respectively

Data are expressed as the mean ± SD

[a] Koyama's classification of MTS [11]

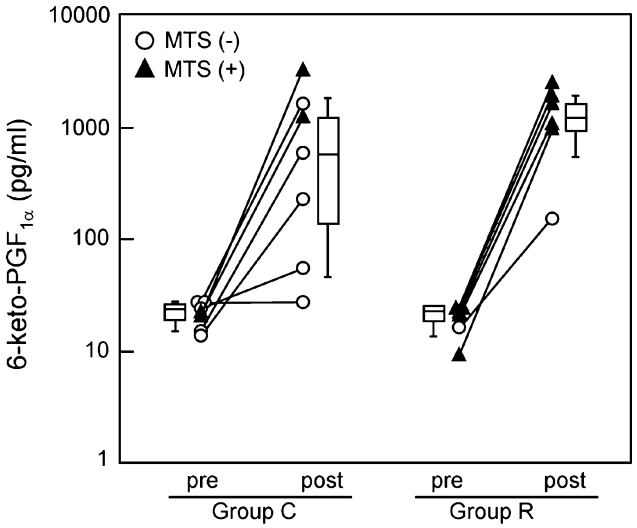

Fig. 3 Plasma concentrations of 6-keto-$PGF_{1\alpha}$ (pg/mL) in group C and group R during anesthesia. Blood samples were taken before skin incision (*pre*) and 20 min after skin incision (*post*). Values are given as *box-plots* displaying the median and 10th, 25th, 75th, and 90th percentiles. *Open circle* MTS did not appear, *filled triangle* MTS appeared

surgery or major abdominal surgery [1–5]. In this study, MTS appeared more often in laparotomy than in laparoscopic surgery in both groups. This may be due to differences in mesenteric traction, which is stronger and causes more shear stress in laparotomy than in laparoscopic surgery [12].

Critical MTS was defined as facial flushing with hypotension and tachycardia (Level 2). In this study, 14 of 18 patients (78%) undergoing laparotomy in group R were diagnosed with critical MTS (Level 2), whereas four patients were diagnosed with MTS with facial flushing only (Level 1). In comparison, three of four patients (75%) undergoing laparotomy in group C were Level 2, and there was only one case of Level 1. There was no difference in hemodynamic changes in MTS cases between both groups, suggesting that the severity of MTS was not dependent on the use of remifentanil.

In our study, it was the anesthesiologist who made the diagnosis of MTS based on the symptoms of facial flushing and hemodynamic changes. The main symptoms of MTS, such as hypotension, tachycardia, and skin flushing, can also be observed as an anaphylactic reaction. However, in our study, a differential diagnosis was possible because the symptoms of MTS appeared just when the surgeons performed mesenteric traction after the incision of the peritoneum and exploration of the abdominal cavity. Moreover, previous studies have reported that the frequency of anaphylactic reaction during general anesthesia is no higher than 0.02–0.03% [13, 14]. No other clinical symptoms fit the timing and symptomatology as well as MTS.

We found that remifentanil facilitated the incidence of MTS. However, there was no evidence showing whether remifentanil directly acted on the onset of MTS.

It has been reported that the production of PGI_2 might be induced by remifentanil [10] as well as by nitric oxide in endothelial cells. Remifentanil suppresses the sympathetic nervous system [15, 16] and inhibits calcium channels in human mesenteric arteriolar smooth muscle cells [17].

The use of opioids, such as fentanyl and remifentanil, result in systemic vasodilation. The occurrence of MTS may be promoted by the vasodilation mediated by the synergistic or additive effects of remifentanil.

In group C, the mean dose of fentanyl for 30 min after skin incision was significantly higher in patients developing MTS (+) than in those who did not [MTS (−)]. It is generally considered that the higher dose of opioids suppresses the sympathetic nervous system in addition to dominantly activating the parasympathetic nervous system. Under this condition, peripheral vasodilatation may be promoted with mesenteric traction. Because the predictive value of effect-site concentration of opioids in group R was higher than that in group C in this study, we observed a higher incidence of MTS in group R patients than in group C patients. However, there was no relation between the dosage of remifentanil and the incidence of MTS in group R patients. MTS appeared in many—but not all—cases with the use of remifentanil in laparotomy because differences in the sensitivity of each patient or in the strength of mesenteric traction in each surgery may have affected the incidence of MTS.

To demonstrate the increase in the plasma concentration of 6-keto-$PGF_{1\alpha}$, a stable metabolite of PGI_2, as a diagnostic marker for the diagnosis of MTS, we examined the concentration of this substance in arterial blood taken before and 20 min after the skin incision from 13 randomly selected patients. The baseline concentration of 6-keto-$PGF_{1\alpha}$ was low, and there was no difference between the groups. Therefore, the use of remifentanil alone does not increase the concentration of 6-keto-$PGF_{1\alpha}$.

Although previous studies have reported significant correlations between 6-keto-$PGF_{1\alpha}$ level and systemic vascular resistance, cardiac output, and the level of facial flushing during mesenteric traction [1, 7, 18], we found no significant correlation between the plasma 6-keto-$PGF_{1\alpha}$ concentration and hemodynamic changes in the limited number of patients enrolled in our study.

It is still questionable whether there is a statistically significant difference in the plasma concentration of 6-keto-$PGF_{1\alpha}$ with or without remifentanil. The time-dependent change in the plasma concentration of 6-keto-$PGF_{1\alpha}$ should also be examined, as should other factors that might affect MTS induced by remifentanil, such as NO and histamine.

This study has a number of limitations. First, the diagnosis of MTS was dependent on the assessment of each anesthesiologist. There is no evident diagnostic criteria for MTS, except for the confirmation of elevated plasma PGI_2 levels. However, the evaluation of MTS was confirmed with a review of each anesthetic record by a second anesthesiologist. Second, we excluded patients who were medicated with NSAIDs, but we did not exclude those using any other medication, such as antihypertensive drugs or antiarrhythmic drugs. There was no significant tendency of the incidence of MTS, even with or without these medications, before surgery. Third, the sample size for the analysis of plasma 6-keto-$PGF_{1\alpha}$ was also small. There were only six or seven cases of each group in our study. This small sample size probably decreased the statistical power to detect differences. Further study with a larger sample size is needed. Taken together, extensive prospective studies are necessary to establish the apparent relationship between MTS and remifentanil.

In conclusion, we demonstrated that the incidence of MTS during laparotomy increased with the use of remifentanil. This suggests that remifentanil has some effects on the trigger for MTS. MTS should therefore be taken into consideration when hypotension and tachycardia suddenly occur during the early stage of laparotomy under general anesthesia using remifentanil.

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